REMARKS

Claim 1 is amended. Claims 8-10 are cancelled in favor of new Claims 11-22. Claims 1-7 and 11-22 are pending. Favorable reconsideration is respectfully requested.

At the outset, Applicants thank Examiner Anderson for indicating that the amendment would further favorable prosecution of the present application and for helpful comments during the discussion held on October 21, 2002, and in the Office Action for overcoming the rejections.

The rejection of Claims 1-10 under 35 U.S.C. § 103(a) over US 5,061,717 (US'717) and EP 0 846 693 (EP'693) or in any combination is traversed below.

At best, US'717 discloses a thiazolidinedione. However, US'717 fails to disclose that the thiazolidinedione containing a methoxy substituent on a benzamide ring.

At best, EP'693 discloses a benzyldioxothiazolidylbenzamide compounds. However, EP'693 fails to disclose that the benzylthiazolidione compound contains a CH_2NHCO phenyl, phenoxy, or benzyloxy at a site equivalent to A in formula (I) in Claim 1.

The claimed invention relates, in part, to benzylthiazolidine-2,4-dione derivatives that may contain a methoxy substitutent as R3 in formula (I) (see Claim 1 above). Further, the claimed compounds may contain a phenyl, phenoxy, or benzyloxy at the position A.

The Office contends it would be obvious to obtain the claimed compounds by substituting the benzylthiazolidine-2,4-dione compounds disclosed in US'717 with the methoxy substituents disclosed in EP'693. Motivation to modify the disclosure of

one reference must be expressly found in the disclosures of the cited references themselves or well within the knowledge of the skilled artisan. The Office contends that this motivation is "to create other useful the benzylthiazolidine-2,4-dione compounds useful as blood glucose lowering drugs". The Office does not provide references demonstrating that the skilled artisan would have known to make a benzylthiazolidine-2,4-dione compound containing a methoxy as R3 and phenyl, phenoxy, or benzyloxy as A in formula (I). In fact, the Office merely states a conclusion absent any evidence. Further, there is not one disclosure found in any of the cited references suggesting that it would be desirable to modify a benzylthiazolidine-2,4-dione compound contain a methoxy as R3 and phenyl, phenoxy, or benzyloxy as A in formula (I). Of course, the skilled artisan may wish to find additional benzylthiazolidine-2,4-dione compounds useful as blood glucose-lowering drugs. In fact, any compound useful as blood glucose-lowering drug are desirable. The key is that there is no guide found in any one of the references to modify there disclosures in a specific manner to obtain the claimed compounds. Further, the Office is reminded that it is not permitted to use the present specification as a guidepost to combine the disparate disclosures of the cited references (see In re Vaeck 20 USPQ 2d 1438).

In light of the above, none of the references disclose or suggest the claimed compounds. Further, there is no motivation found in any of the references to modify the disclosures therein to obtain the claimed compounds. Accordingly, no *prima facia* case of obviousness can possibly exist; and therefore, withdrawal of these grounds of rejection is respectfully requested.

In arguendo, if the Office maintains that a *prima facia* case of obviousness does exist, Applicants respectfully submit that none of the references provide

sufficient specificity in the disclosures therein to obtain the claimed compounds. Further, one reading these disclosures would not have expected the surprisingly superior results of the claimed compounds. The Applicants provide herewith, Exhibit A, which is a set of experiments comparing the efficacy of compounds 17, 22, 23, and 28 disclosed by EP'693 with compounds 1-3 embodied by the claimed invention in their abilities to exhibit lipid-lowering action based upon their agonist activities on PPAR (human peroxisome proliferator-activated receptor) alpha and their blood sugar-lowering action based on their agonist activity on PPAR gamma.

The Office is reminded that the Examiner suggested that such a comparative data study be submitted in support of the patentability of the claimed invention. At the above-mentioned Interview, the Examiner specifically requested comparative data provided for the above compounds. It should be noted that the Examiner also requested comparative data for compound 38 of EP'693. However, the study could not be performed because the stock amount of this compound was too small to perform such experiments.

As an overview, the data in Exhibit A clearly demonstrate that the claimed compounds are superior in their dual agonist activity on PPAR alpha and gamma. In Table 3 of the present specification (reproduced as Table A in Exhibit A), it is clearly demonstrated that the claimed compounds show strong transactivation to both PPAR alpha and gamma. The same experimental conditions were used test the transactivation activities of the compounds 17, 22, 23, and 28 disclosed by EP'693 (see Table B in Exhibit B). The data of Table B demonstrates that, although compounds 17, 22, 23, and 28 disclosed by EP'693 are capable of activating PPAR gamma, they can not activate PPAR alpha even al concentrations as high as 10 μmol/L.

In direct contrast to the compounds disclosed by EP'693, the claimed compounds are capable of activating PPAR alpha quite readily. Further, the claimed compounds are capable of strongly activating PPAR gamma. Therefore, the claimed compounds are clearly superior in their surprising dual agonist capabilities with regards to PPAR alpha and gamma compared to the compounds disclosed by EP'693. Accordingly, the claimed compound may have both lipid-lowering and blood glucose-lowering capabilities, while those disclosed by EP'693 can not.

In light of the above discussion and Exhibit A attached hereto, it is clear that none of the cited references provide sufficient specificity to make the claimed compounds. Further, Applicants have provided data in Exhibit A (as requested by the Examiner) which clearly demonstrates the surprisingly superior qualities of the claimed compounds (e.g. dual agonist activating activity of PPAR alpha and gamma).

The rejection of Claims 1 and 8-10 under 35 U.S.C. § 112, second paragraph, is obviated by the cancellation of Claims 8-10. The Office's attention is drawn to new Claims 11-22 which are not duplicates of Claim 1 where the method claims contain a positive active step. Further, Claim 1 is amended to remove the parentheses. Accordingly, withdrawal of this ground of objection is respectfully requested.

The objection to Claims 8-10 is obviated by the cancellation of these claims. The Office's attention is drawn to new Claims 11-22 which are not duplicates of Claim 1 where the method claims contain a positive active step. Accordingly, withdrawal of this ground of objection is respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance. Favorable reconsideration is respectfully requested. Should anything further be required to place this application in condition for allowance, the Examiner is requested to contact Applicants' Attorney by telephone.

Respectfully submitted,

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HEREWITH

IN THE CLAIMS

Please amend the claims as follows.

--Claims 8-10 are canceled.--

--1. (Amended) A [Substituted] substituted benzylthiazolidine-2,4-dione [derivatives] derivative represented by a general formula (1)

(1)

[[]wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents[]], their medicinally acceptable salts and their hydrates.--

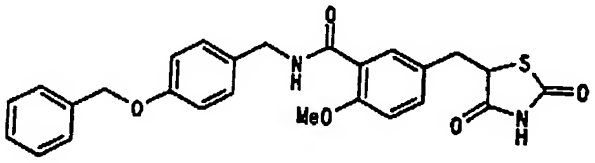
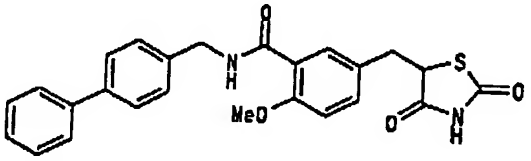
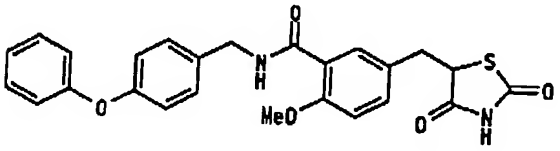
--Claims 11-22 are added.--

2) The comparative experimental data, which are requested by the Examiner, have been prepared as described under.

The present invention submits the compound having agonist activity of human peroxisome proliferator-activated receptor (PPAR) and has been developed on the expectation of exhibiting lipid-lowering action based on agonist activity of PPAR alpha in addition of blood sugar-lowering action based on agonist activity of PPAR gamma. That is, the present invention has developed a dual agonist capable of activating PPAR alpha and gamma.

In Table 2 of the present specification, it is described that the Example compounds of the present invention show the strong transactivation to the both of PPAR alpha and gamma in addition to the activation of PPAR alpha. The data of transactivation of the present compound are transferred from the specification as under.

(Table A) Transactivation of the present compound

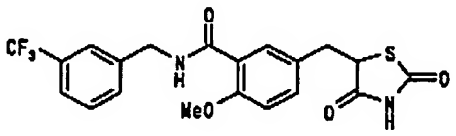
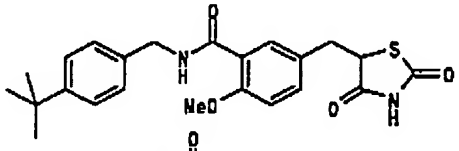
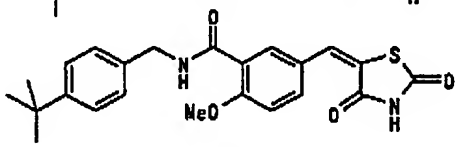
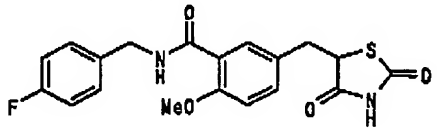
Example No.	Structure	Transactivation PPARα EC_{50} (μmol/L)	Transactivation PPARγ EC_{50} (μmol/L)
1		0.44	-
2		0.63	6.8
3		0.24	0.24

From this result, it is demonstrated that the compounds wherein A in the general formula (1) of the present invention denotes benzyloxy group, phenyl group or phenoxy group have the activation action to PPAR alpha and the compounds of Examples 2 and 3 have also the activation activity to PPAR gamma.

Next, the tested result of the transactivation by the same experiment concerning Examples 17, 22, 23, 28 of the cited reference EP 0 846 693 is

shown below (the data of Example 38 is also requested, but the data thereof could not be derived, because the amount of said sample was too small therefor).

(Table B) Transactivation of the cited reference compounds

Example No.	Structure	Transactivation PPAR α EC_{50} (μmol/L)	Transactivation PPAR γ EC_{50} (μmol/L)
17		>10	0.18
22		>10	0.23
23		>10	0.50
28		>10	0.20

As this result, the cited reference compounds, although strong in activation to PPAR gamma, are considered to be very weak in activation to PPAR alpha, because it is not recognized in the level of 10 micro-mol/L. The cited reference compounds are mainly the agonist of PPAR gamma.

On the other hand, it is obvious that the present invention compounds significantly have the activation to PPAR alpha and/or have significantly the activation to PPAR gamma in addition to that to PPAR alpha.

The present invention compounds are the alpha agonist and/or the dual agonist having activating PPAR alpha and/or the both of PPAR alpha and gamma.

Accordingly, the present invention compounds are expected to exhibit lipid-lowering action based on PPAR alpha together with blood sugar-lowering action based on PPAR gamma.

3) Our comment

The present invention concerns the compound having agonist activity of human peroxisome proliferator-activated receptor (PPAR) and has developed a dual agonist which can activate PPAR alpha and gamma with expecting the manifestation of lipid-lowering action based on PPAR alpha agonist together with blood sugar-lowering action based on PPAR gamma agonist (a part of them is the compound of not being dual).

Comparing the PPAR activation data of the cited reference with the activation data of the present invention, we can demonstrate the existence or the non-existence of PPAR alpha activity.

The present invention compounds which are strong in activating both of PPAR alpha and gamma are expected to exhibit the effect on the aspect of lowering function of lipid, which have the excellent characteristics in comparison with the cited reference compounds.